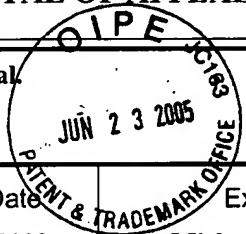


## TRANSMITTAL OF APPEAL BRIEF (Large Entity)

Docket No.  
PZ9947

In Re Application Of: Gill, et.al.



Application No.

10/069,691

Filing Date

June 3, 2002

Examiner

Michael G. Hartley

Customer No.

36335

Group Art Unit

1616

Confirmation No.

3741

Invention: Improved Container Composition for Radiopharmaceutical Agents

COMMISSIONER FOR PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed on

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Signature

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of : Gill et al.  
Application No. : 10/069,691  
Filing Date : June 3, 2002  
Art Unit : 1616  
Title : Improved Container Composition for Radiopharmaceutical Agents  
  
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APPEAL BRIEF

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*Lori A. Maize*

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*June 21, 2005*

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**I. REAL PARTY IN INTEREST**

The real party in interest in this Appeal is Amersham plc (now part of General Electric “GE”).

**II. RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences.

**III. STATUS OF CLAIMS**

Claims 1-14 are pending in this application. The Examiner has rejected all of these claims. Claims 1-14 as amended during prosecution are reproduced in **Appendix A** attached hereto. Appellants are appealing the rejections of Claims 1-14.

**IV. STATUS OF AMENDMENTS**

Appellants filed an Amendment on December 21, 2004 and an advisory action was mailed on January 18, 2005. No claims were amended subsequent to the Examiner’s final rejection that was mailed on October 26, 2004.

**V. SUMMARY OF CLAIMED SUBJECT MATTER**

Independent Claim 1 describes a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface wherein the radiopharmaceutical includes a metal complex.

Independent Claim 6 describes a kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.

Independent Claim 10 describes a composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises a stabilizer suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

Independent Claim 11 describes a composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

## **VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

The issues for review in this appeal arise from a Final Rejection that was mailed on October 26, 2004. The Examiner rejected claims 1-14 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,961,952 ("Crane") in view of any one of JP 11099192 ("JP '192") or DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther").

Therefore, the issues in this appeal are:

1. Whether Crane in view of JP '192, Schott Glaswerke, or Walther individually or in combination, discloses or suggests all the elements of the following claims:
  - a. Claims 1-5,
  - b. Claims 6-9,

c. Claim 10, and

d. Claims 11-14?

2. Whether Crane in view of JP '192, Schott Glaswerke, or Walther contain a motivation to combine one reference with the other reference?

## **VII. GROUPINGS OF CLAIMS**

In accordance with 37 CFR 1.192(c)(7), the Appellants state that the four separately grouped claims 1-5, 6-9, 10, and 11-14 do not stand or fall together.

## **VIII. ARGUMENT**

The Examiner rejected Claims 1-14 under 35 U.S.C. § 103 (a) as being unpatentable over U.S. Patent No. 5,961,952 ("Crane") in view of any one of JP 11099192 (JP '192) or DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther").

Furthermore, the Examiner alleges that:

"Clearly, the use of silicon [*Emphasis added*] coated vials is a known advantage in the field of pharmaceuticals and radiopharmaceuticals, and therefore one skilled in the art would obtain these benefits for various pharmaceuticals and/or radiopharmaceuticals, such as, those disclosed by Crane. Therefore the motivation to combine arises from the benefits of the prior art".

Appellants respectfully point out that the Examiner refers to 'silicon' coatings at least 8 times in his Office Action dated October 26, 2004. Such repeated use of this term cannot be explained away as an isolated typographical error. Silicon is the chemical element Si, whereas the present claims refer to silica which is silicon dioxide or SiO<sub>2</sub>. Clearly combinations

which teach towards silicon coatings teach away from the present invention. The two cannot be treated as interchangeable, since they are chemically very different.

The Board of Patent Appeals and Interferences (“Board”) should reverse the Examiner’s rejections since Crane in view of JP ‘192, Schott Glaswerke, or Walther taken as a whole, fails to disclose, teach, or suggest the present invention. Moreover, a proper combination of the references would, at best, teach away from the present invention.

**A. The Examiner’s Rejections of the Claims Should be Reversed Since Crane, JP ‘192, Schott Gaswerke, and Walther, Individually or In Combination, Fail to Teach All the Elements of the Claims**

The present invention is directed to a composition comprising a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. The present invention also relates to non-radioactive, preferably lyophilized kits for the preparation of radiopharmaceutical metal complexes, where the kit composition is supplied in a container which has a silica coating on the inner surface.

Crane simply discloses a method of using a metal complex and its analogs to diagnose or radioimage breast tumors. Crane only provides a vague reference to the use of a vial to hold its compounds. More importantly, Crane does not even disclose, teach, or suggest using any type of coating on the inner surface of the vial. Hence, the Appellants respectfully submit that Crane fails to provide any motivation for improving the vial, let alone the inner surface for its compounds.

JP '192 discloses that silica-coated vials (prepared by a chemical coating and pyrolysis method), are useful to prevent adsorption of radiopharmaceutical products such as a thallium chloride, ( $^{201}\text{Tl}$ ), solution to the surface of a glass. JP '192 provides no description of using metal complexes as radiopharmaceuticals. Furthermore, the present invention defines the term 'metal complex' as a coordination complex of a metal (M) with an organic ligand (L). This is to be contrasted with an uncomplexed or free metal ion such as the monovalent thallium cation,  $\text{Tl}^+$ , used in JP '192.

Schott Glaswerke discloses that glass containers having an internal coating of  $\text{SiO}_2$ , prepared by a plasma chemical vapour deposition process, are useful for the storage of pharmaceutical or diagnostic solutions. However, Schott Glaswerke provides no further description of a contained material such as radiopharmaceutical metal complexes, let alone a radiopharmaceutical, other than the generic reference to 'pharmaceutical'.

Walther discloses a glass tube with an oxide coating. Walther notes that the prior art taught a silica-coated tube for use with (generically) pharmaceuticals. Walther contains no reference to radiopharmaceutical metal complexes per se.

Appellants contend that no motivation to combine exists because Crane itself does not teach or suggest that the radiopharmaceutical metal complexes described therein suffer from any leaching problems, hence no expectation of using silica-coated vial containers exists. Hence, the (unspecified) 'problem being solved' suggested by the Examiner does not exist within Crane itself. Additionally, the Examiner's argument that the secondary references are 'reasonably



pertinent to the problem' is vague and not the standard applied by the USPTO for an obviousness attack – which requires motivation based on a clear expectation of improved results for the specific combination be demonstrated.

Appellants also submit that the present invention describes at length how radiopharmaceutical metal complexes suffer from unforeseen or variable problems which are solved using silica-coated vials. See page 4, line 17 to page 9, line 23 of the present specification. None of these problems were recognized in the prior art, and hence the cited references simply cannot provide a motivation to apply silica-coated vials to radiopharmaceutical metal complexes. The solution to the problem provided by the present claims is believed non-obvious for this reason.

Furthermore, the invention as taught by Crane at Columns 7 and 8 has many features: e.g.

*tert*-butyl Isonitrile ligand

$^{99m}\text{Tc}$  or  $^{186}\text{Re}/^{188}\text{Re}$  metal complex thereof

solubilization aid

reducing agent

pharmaceutically-acceptable carrier

a non-radioactive *tert*-butyl isonitrile metal complex precursor

pharmaceutically-acceptable filler

vial

lyophilization aids

buffers

stabilization aids

bacteriostats

transfer ligand,  
etc.

Of all of these features, the Examiner states that it is the *vial* which the person skilled in the art would address to ‘improve’ on Crane. It is well settled that a reference must be considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird*, 16 F.3d 380, (Fed. Cir. 1994). The Examiner’s reasoning ignores the fact that Crane gives no description, at all, about the inner surface wall of the vial but expounds at length about the other features of the invention. In fact, Appellants respectfully submit, that Crane’s inclusion of the vial is not a key contribution to the invention disclosed by Crane. The Examiner fails to demonstrate why one of ordinary skill in the art, upon reading Crane, would be motivated to select the vial – of all things – as the key to ‘improving’ Crane. Appellants contend that the Examiner has failed to show why the person skilled in the art would select only the vial from this long list of features to seek to improve, and as a consequence choose not to improve all the other aspects even those which Crane teaches as important. Furthermore, why would the person skilled in the art choose specifically silica-coated vials, when a great variety of alternative coatings (e.g. including silicon-containing polymers such as silicones or silanes) were available, in regular use, each also having “benefits”. In this respect the Appellants respectfully submit that the Examiner has failed to make a *prima facie* case of obviousness in rejecting the present invention.

Furthermore, a *prima facie* case of obviousness requires that motivation for the skilled artisan to modify or combine specific references exists. The Examiner’s own statements [Office Action, October 26, 2004] refer to “various pharmaceuticals and/or

radiopharmaceuticals” and “such as, those disclosed by Crane” and “reasonably pertinent to the problem being solved”. These statements, however fail to address the key criterion of why the person skilled in the art would specifically choose Crane to combine with, and hence where the motivation exists to apply, the silica-coated containers to radiopharmaceutical metal complexes. It is not clear exactly what the specific “benefits” expected for radiopharmaceutical metal complexes would be. The Examiner’s own statements seem to suggest that the person skilled in the art *could* apply the silica-coated vials to *any* radiopharmaceutical, of which Crane is merely illustrative. However, to state that one ‘could’ combine references is not the standard for making a prima facie case of obviousness as such a standard would only grant patentability to combinations which ‘could not’ be made. Indeed, if the Examiner’s logic was followed, then all radiopharmaceuticals would be provided in silica-coated vials, once the cited prior art in question had published, and no one would contemplate using uncoated vials, since it would be folly to ignore the purported ‘benefits’. In reality, uncoated vials are still very much the norm for radiopharmaceuticals and coated vials (in any form), the exception. This is because coated vials are significantly more expensive, and no one would accept the additional costs for unspecified “benefits” that were not clearly identified as necessary for the specific product. Accordingly, Appellants respectfully disagree with the Examiner’s basis for finding a motivation to combine references.

The Examiner argues that the person skilled in the art would be motivated to combine Crane and JP'192 to solve absorption problems. Crane, however, specifically teaches "solubilization aids" as an essential feature to solve this problem described therein:

Column 2 lines 33-47 and 56-57,  
Column 3 lines 23-33 and 46-47,  
Column 7 lines 1-26.

The logic of the Examiner's combination is that the 'solubilization aid' taught by Crane would no longer be necessary, since the coated vial would (presumably) solve the absorption problem. This contradicts the teaching of Crane, in that the absence of the 'solubilization aid' would remove an essential teaching of Crane. Accordingly, combining Crane and JP '192 in this manner is an invalid combination.

Additionally, even assuming, *arguendo*, that the references are properly combinable; Appellants respectfully submit that any such combination would teach away from the present invention. 'Teaching away' simply means teaching a solution that would not lead to the claimed subject matter. As noted by the Federal Circuit:

A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. (emphasis added).

*Para-Ordnance Mfg. v. SGS Importers Int'l*, 73 F.3d 1085 (Fed. Cir. 1995).

Appellants respectfully submit that the mere fact that a reference may suggest an 'improvement' does not dictate that the improvement will direct one to all other 'improvements'. That is, one improvement can teach away from another, as the two improvements may diverge

from each other in their teachings. The *Para-Ordinance* decision (above) clearly states that teaching away does not require a negative teaching in the prior art, the prior art need only teach other, divergent, solutions to be deemed to teach away from an invention.

Thus, by teaching positively towards certain embodiments or features as being important or preferred, the art provides a motivation for the person skilled in the art to go in a particular direction. If that direction leads towards subject matter outside the scope of the claims at issue, then it constitutes a “teaching away”. Appellants maintain that the person skilled in the art, even if assumed to be contemplating improvements of Crane, would focus on the specific teachings in Crane of embodiments taught to be important, and be motivated to improve those elements. Crane teaches that a method of using a metal complex and its analog to diagnose or radioimage breast tumors to be important. Again, per *Baird*, it is well settled that a reference must be considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird supra*. Crane is clearly directed to the use of radiopharmaceutical metal complexes as breast tumor diagnosing or imaging agents, which is described at length from Column 2 line 7 to Column 5 line 21. That is, Crane devotes about four columns of text to what is the essence of his invention, the metal complexes, and not to improved containers for those metal complexes. Again, Crane itself does not discuss the features of the containers used for the compounds, and hence gives no weight to that feature. Crane’s emphasis on using metal complexes as breast tumor diagnosing or imaging agents, and the apparent satisfaction with the conventional (ie. uncoated) vial would indicate that improvements to the metal complexes as breast tumor diagnosing or imaging agents are found by

adjusting the formulation of the metal complexes and/or diagnosing or imaging agents, not by modifying the vial.

Accordingly, as none of the cited references are properly combinable so as to render the present invention obvious, Appellants respectfully request that the Board reverse the Examiner's rejections and direct that claims 1-14 be allowed.

**B. Claims 1, 6, 10, and 11 are Separately Patentable**

Independent claims 1, 6, 10, and 11 are separately patentable from the prior art.

Unlike Crane in view of JP '192, Schott Glaswerke or Walther, claim 1 teaches an improvement of a composition which comprises a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. Crane does not even disclose, teach, or suggest using a composition in combination with a coating on the inner surface of the vial. Additionally, JP '192 provides no description of using metal complexes as radiopharmaceuticals nor does it disclose, teach, or suggest preparing the silica-coated vials by a plasma chemical vapour deposition (PCVD) process. Furthermore, Schott Glaswerke provides no further description of a contained material such as radiopharmaceutical metal complexes, let alone a radiopharmaceutical, other than the generic reference to 'pharmaceutical'. Likewise, Walther notes that the prior art teaches a silica-coated tube that can be used with generic pharmaceuticals but does not disclose, teach, or suggest any reference to radiopharmaceutical metal complexes let alone the combination of using silica-coated tubes with radiopharmaceutical metal complexes.

In another light, claim 6 teaches the use of a kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica-coated inner surface. Crane in view of JP '192, Schott Glaswerke or Walther do not even disclose, teach, or suggest using a kit claim for the preparation of a radiopharmaceutical metal complex. use in combination with a coating on the inner surface of the vial.

Additional claim 10 further teaches another use for a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. Claim 10 discloses a composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises a stabilizer capable of stabilizing said radiopharmaceutical metal complex and an organic ligand which forms a coordination complex with the metal in a container which has a silica coating on the inner surface. Crane in view of JP '192, Scott Glaswerke or Walther do not even disclose, teach, or suggest using the present invention composition claim 10.

Finally, claim 11 teaches yet another use of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. Crane in view of JP '192, Schott Glaswerke or Walther do not even disclose, teach, or suggest using the present invention composition claim 11.

Accordingly, claims 1, 6, 10, and 11 are separately patentable from the prior art.

### VIII. CONCLUSION

In view of the foregoing, Appellants respectfully request that the Board reverse the rejections of Claims 1-14 as set forth in the Office Action mailed October 26, 2004, that the Board allow the pending claims since they are in condition for allowance, and that the Board grant any other relief as it deems proper.

Dated: June 21, 2005

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Craig M. Bohlen', is written over a horizontal line.

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## APPENDIX A

1. In a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, the improvement comprising the radiopharmaceutical includes a metal complex.
2. The composition of claim 1 wherein the radiopharmaceutical is a liquid or solution.
3. The composition of claim 1 wherein the metal of the metal complex is  $^{111}\text{In}$  or  $^{99\text{m}}\text{Tc}$ .
4. The composition of claim 1 wherein the silica coating is deposited by a PCVD process.
5. The composition of claim 1 wherein the container is a glass vial with a closure.
6. A kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.
7. The kit of claim 6 wherein the metal complex is a  $^{99\text{m}}\text{Tc}$  complex.

8. The kit of claim 6 wherein the non-radioactive organic ligand composition is lyophilised.
9. The kit of claim 6 wherein the silica coating is deposited by a PCVD process.
10. A composition for the preparation of a stabilised radiopharmaceutical metal complex which comprises (i) a stabiliser capable of stabilizing said radiopharmaceutical metal complex; and (ii) an organic ligand which forms a coordination complex with the metal; in a container which has a silica coating on the inner surface.
11. A composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.
12. The composition of claim 11, wherein the bacteriostat comprises a paraben.
13. The composition of claim 10 wherein the metal of the metal complex is  $^{111}\text{In}$  or  $^{99\text{m}}\text{Tc}$ .
14. The composition of claim 10 wherein the silica coating is deposited by a PCVD process.